May 26, 2026

Dear Friends,

As the spring season turns into early summer here in St. Louis, I am writing to share several updates that I have been looking forward to sending for a long time. Thank you, as always, for being part of the Wolfram syndrome community. Your trust, patience, and partnership mean a great deal to my team and to me. Everything we do in the clinic, the clinical trial unit, and the laboratory is guided by one shared goal: CURE4WOLFRAM. The past few months have brought meaningful progress on three fronts that I would like to walk through with you, because each one represents a step that, in different ways, our community has been waiting for.

Phase 2 Clinical Trial of AMX0035 (PB&TURSO): Published in The Journal of Clinical Investigation

I am very happy to share that the results of our Phase 2 HELIOS trial of sodium phenylbutyrate and taurursodiol (AMX0035, PB&TURSO) in Wolfram syndrome have now been published in The Journal of Clinical Investigation. This is, to the best of our knowledge, the first positive clinical trial in the history of Wolfram syndrome research. After many years of careful laboratory science, natural history studies, and trial design, seeing these results in a peer-reviewed journal feels like a turning point for our field.

The trial enrolled 12 adults with genetically confirmed Wolfram syndrome and insulin-requiring diabetes. Over 24 and 48 weeks of open-label treatment, we observed overall improvement from baseline in C-peptide response during a mixed-meal tolerance test, which is our primary measure of remaining pancreatic beta cell function. We also saw improvement in HbA1c and time in target glucose range, and best-corrected visual acuity trended toward stabilization over 48 weeks, which is meaningful given the progressive nature of Wolfram syndrome. All participants with available data were classified as responders on both the Participant and Clinician Global Impression of Change scales at weeks 24 and 48. PB&TURSO continued to show a favorable safety profile, with adverse events that were mild or moderate and mostly gastrointestinal, and no serious treatment-emergent adverse events or discontinuations.

I want to be careful and clear-eyed about what this means. This was a single-center, single-arm, open-label study in a small number of participants, reflecting the rarity of Wolfram syndrome. We cannot draw conclusions about long-term disease modification from a Phase 2 trial alone. What we can say is that the results support continued development of PB&TURSO and provide

the foundation we need to plan next steps responsibly. We are working closely with Amylyx Pharmaceuticals on those next steps, and we will share more as soon as we are able.

This work would not have been possible without the trust of the participants and families who made the long journey to St. Louis again and again, and without the steady support of the Wolfram syndrome community around the world. Thank you.

Publication: Phase II trial of sodium phenylbutyrate and taurursodiol in Wolfram syndrome. J Clin Invest. 2026;136(10):e198519.

Understanding the Earliest Cause of Vision Loss in Wolfram Syndrome

Alongside the clinical trial work, our laboratory has also published a new study in Frontiers in Neuroscience that addresses one of the questions I am asked most often by families: why does vision change before we can see clear damage in the optic nerve, and what can we do about it earlier?

In this study, we carefully examined the retina and optic nerve of a Wolfram syndrome mouse model at 4 and 7 months of age. What we found is that the earliest detectable change in the visual system is not the loss of retinal ganglion cells, and not loss of the cell bodies or dendrites, but a quiet uncoupling and loss of the synaptic connections themselves, specifically on the presynaptic side. These synaptic alterations are already present at 4 months, well before significant axonal loss in the optic nerve becomes detectable at 7 months. In other words, the cells are still there, but the connections between them are weakening first.

This matters for two reasons. First, it gives us a clearer picture of when the disease process actually begins in the visual system, which is earlier and more subtle than many imaging studies would suggest. Second, and more importantly for our patients, it identifies early synaptic preservation as a promising therapeutic target. If we can protect or restore those synapses, we have a real opportunity to intervene before irreversible axonal loss occurs. This is the scientific foundation that we are now using to design and prioritize our regenerative and gene-based therapies for vision.

Publication: Synaptic alterations are preceding the axonal loss in optic atrophy of Wolfram syndrome mouse model. Front Neurosci. 2026.

GLP-1 Receptor Agonists in Wolfram Syndrome: A New Preprint

Many families have asked me about GLP-1 receptor agonists, a class of medications that has received a great deal of attention in recent years for diabetes and other conditions. We have been studying this class carefully in Wolfram syndrome models for some time, because GLP-1 receptor activation has biologically plausible benefits for pancreatic beta cells and for neurons, both of which are affected in Wolfram syndrome.

We have now posted a preprint on medRxiv summarizing our work on GLP-1 receptor agonists in Wolfram syndrome. A preprint is a manuscript that has been shared publicly before peer review is complete, so that the community can read it, learn from it, and provide feedback while the formal review process moves forward. I want to be transparent that the findings in this preprint are still undergoing peer review, and the final published version may change in response to that review. I am sharing it now because I believe the questions it addresses are important to families, and because openness is a core value of our team.

Our broader hope is that this work, together with the AMX0035 results and our ongoing gene-editing and regenerative therapy programs, will help us build a layered, individualized treatment strategy for Wolfram syndrome rather than relying on any single approach.

Preprint: GLP-1 Receptor Agonists in Wolfram Syndrome. medRxiv 2026.03.31.26349885.

Where This Leaves Us

Taken together, these three publications represent a meaningful moment for our field. We now have the first positive Phase 2 clinical trial result published in a peer-reviewed journal, a much clearer understanding of the earliest biological event that drives vision loss, and a publicly available preprint that adds to the evidence base for a class of medications already familiar to many families. None of these, on its own, is a cure. Each, however, brings us closer. Alongside these publications, our other major programs continue to move forward, and I would like to share where each of them stands.

Gene-Editing Therapy: Addressing the Root Cause

Because Wolfram syndrome is caused by pathogenic changes in the WFS1 gene, correcting those changes has the potential, in theory, to address multiple aspects of the disease at their source. Over the past several months we have made particularly strong progress on this front. Using patient-derived induced pluripotent stem cells, which can be differentiated into many cell types, we have successfully corrected WFS1 pathogenic changes in laboratory-generated brain cells in the tissue culture dish. After correction, these cells show improved survival, healthier

energy production, reduced oxidative stress, and more stable calcium balance. We are seeing similar encouraging improvements in insulin-producing beta cells derived from patient cells.

At the same time, we are working intensively on one of the most critical challenges in gene editing: safe and effective delivery. Our current focus is on developing novel delivery systems for the brain and eye. Rather than relying only on conventional approaches such as AAV or peptides, we are investing significant effort in nanoparticles and engineered virus-like particles, which we believe offer a safer and more flexible path forward. Our goal is to build the strongest possible foundation in patient-derived cells and humanized mouse models so that, when we move toward clinical trials, we do so with safety, care, and confidence.

Compound Screening: New Drugs and Supplements

In parallel with gene-based and regenerative approaches, we are actively developing a systematic platform to identify medications and supplements that may benefit individuals with Wolfram syndrome. Using patient-derived induced pluripotent stem cells, we generate brain cells in the laboratory that closely reflect the biology of Wolfram syndrome. These cells allow us to directly test existing drugs, supplements, and new compounds to see whether they improve cell survival, reduce stress responses, support mitochondrial function, or restore healthier cellular balance.

Our highest priorities include antioxidants, sigma-1 receptor agonists, NAD activators, Idebenone, GLP-1 receptor agonists, and other compounds that target endoplasmic reticulum stress and mitochondrial dysfunction. We also have a long list of additional candidates based on scientific rationale and emerging evidence. This platform allows us to evaluate potential therapies in a human, disease-relevant system before moving toward clinical studies. We plan to expand this effort and will continue to share updates as we learn more.

Regenerative Therapy and Neuroprotection

We continue to advance regenerative approaches aimed at protecting vision and the nervous system. One of our key efforts involves a naturally occurring neurotrophic factor called MANF, a molecule that supports cell survival and recovery under stress. MANF is particularly relevant to Wolfram syndrome because it activates pathways that help cells cope with endoplasmic reticulum stress, a major contributor to vision loss and neurodegeneration.

The new findings from our optic atrophy study, described above, are directly informing this work. If the earliest event in vision loss is a quiet weakening of synaptic connections rather than

the death of retinal ganglion cells themselves, then regenerative and neuroprotective strategies have a real window in which to act. With renewed support, our MANF program has regained momentum, and we are steadily generating new data. We plan to share our progress at the next Wolfram syndrome conference.

International Consensus Clinical Guidelines

Our international team of clinicians and scientists continues to develop consensus clinical guidelines for Wolfram syndrome care. We have reviewed more than 350 scientific publications and drafted recommendations spanning genetics, endocrinology, ophthalmology, neurology, urology, gastroenterology, psychiatry, and the transition from pediatric to adult care, with thoughtful input from nearly 50 experts from around the world.

I am happy to share that we have now completed the third round of the structured Delphi feedback process. With each round, the recommendations have become clearer, stronger, and more practical, and we are now finalizing them based on the input from this most recent round. Our team is currently writing the manuscript for publication, so that these guidelines can reach clinicians, families, and healthcare systems around the world in a peer-reviewed form. I am deeply grateful to every collaborator who has contributed to this important effort.

Wolfram Syndrome and Related Disorders Clinic

Our multidisciplinary clinic at Washington University in St. Louis remains committed to providing comprehensive and coordinated care for individuals with Wolfram syndrome and WFS1-related disorders. We continue to prioritize same-day or two-day visits whenever possible for families traveling long distances, including out-of-state and international families. Our nurse navigator, Ashley Raterman, coordinates these efforts and serves as a key point of contact for families.

More information is available at https://wolframsyndrome.wustl.edu/. For appointments and coordination, please contact WolframSyndrome@wustl.edu.

With Gratitude and Determination

When I think back to the early years of this work, the idea of publishing a positive clinical trial in Wolfram syndrome felt, on most days, very far away. The fact that we are here now is because of the courage of patients who joined our studies, the love of families who supported them, and the dedication of clinicians, scientists, and patient organizations around the world who refused to let this disease remain in the shadows. I am profoundly grateful to each of you.

My team and I remain fully committed to this work, every day, with the same urgency that I know our families feel. Thank you for walking this journey with us. Together, I truly believe we are moving closer, step by careful step, to CURE4WOLFRAM.

With gratitude and hope,

Fumi

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